Non-technical Abstract

Proposed Clinical Trial: Transduction of the Upper and Lower Airway Epithelium in Healthy Subjects by an AAV2 Vector that Encodes Human Placental Alkaline Phosphatase

Cystic fibrosis (CF) is a genetic disorder which results in changes in a protein called the cystic fibrosis transmembrane conductance regulator, or CFTR. This change in CFTR affects how salt and water move in and out of the cells in the body, causing an imbalance. As a result, thick mucus develops in the body and can cause many problems, including infections in the lungs and nasal sinuses and blockage of the pancreas and intestines. Treatments for these problems have been beneficial to patients with CF but have not corrected the CFTR defect. Gene therapy aims to correct the CFTR defect by placing a normal gene inside of the cells. The normal gene must be delivered into the cells using another substance which is called a vector. Viruses enter cells easily and are able to carry normal genes into the cells. Different viruses have been tested as vectors in animal and human gene therapy studies. To decide if the vector has worked it is necessary to be able to measure if the cells in the body express the normal CFTR gene. Measurement of the CFTR protein in human cells has been difficult following gene therapy in studies to date.

As a first step in the development of a new CFTR vector system for CF, this research study will use a marker gene, instead of the CFTR gene. The marker gene, human placental alkaline phosphatase (AP), will be delivered with a specific adeno-associated virus (AAV2) vector into the nose of healthy adult subjects. AP can be measured readily in the cells after administration of the vector if the vector has actually entered the cells. The AAV2 vector has been changed in the laboratory so that it does not make any viral proteins and is not expected to cause any viral infection. The purpose of the proposed study is to determine if the AAV2 vector can transfer and express AP in the cells that line the inside of the nose, and in a later study, in the cells that line the airway. The results will be used to plan future studies with other AAV vectors and with the CFTR gene. Subjects enrolled in this study will not benefit from being part of this study. In the future, patients with CF may benefit from the knowledge gained about the possibilities for gene therapy using an altered virus to correct the CFTR defect.